CLINICAL EXPERIENCE WITH FLUOTHANE—1,400 CASES

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In spite of advances in intravenous anesthesia and in conduction analgesia, inhalation techniques have remained the backbone of anesthetic administration throughout the years. Each inhalation drug has some undesirable properties; so the search has continued for better agents to provide safe narcosis for patients. In recent years a particular need has become apparent for a nonflammable and nonexplosive drug which is potent, easily reversible and safe. While screening for such a compound, Suckling in England found a fluorinated ethane derivative, $CF_3CHBrCl$, Fluothane, which Raventós (1) believed could be employed safely in clinical anesthesia. Numerous clinical reports within the last year (2–19) have corroborated the anesthetic properties and nonflammability of this drug.

This report is a sequel to a preliminary investigation (4) and discusses the impressions gained and problems encountered in 1,400 clinical administrations of Fluothane. All age groups were included (table 1) and a variety of surgical procedures performed (table 2).

TABLE 1

Age Groups of Patients Receiving Fluothane

Ages	Number	Per Cent
3 months to 10 years	209	14.9
10 to 19 years	159	11.4
20 to 29 years	214	15.3
30 to 39 years	311	22.2
40 to 49 years	244	17.4
50 to 59 years	153	10.9
60+ years	110	7.9
	1,400	100.0

TABLE 2

Site of Operation

Site	Number	Per Cent
Head and neck	392	28.0
Trunk	182	13.0
Intrathoracic	165	11.8
Intra-abdominal	224	16.0
Pelvic	108	7.7
Extremities	329	23.5
	1,400	100.0

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TABLE 3

LENGTH OF ANESTHESIA AND OPERATION

Time	Number	Per Cent
Less than 1 hour	224	16.0
Less than 2 hours	418	29.9
Less than 3 hours	303	21.6
More than 3 hours	455	32.5
	1,400	100.0

The length of operations was variable (table 3). Several patients received Fluothane on three or four occasions over a three week period.

VITAL FUNCTIONS

Respiratory System.—In light surgical planes of anesthesia, Fluothane depressed the tidal volume of respiration. First intercostal paresis was seen and this was followed by intercostal paralysis. In deeper planes of anesthesia there was weakening and cessation of diaphragmatic action. This respiratory depression developed quickly in three or four minutes when the concentration of the drug was increased rapidly. However, this sequence of events was also easily and quickly reversible. Rate of respiration under Fluothane usually was not altered, although in some patients a tachypnea to a rate of 30 to 35 respirations per minute was seen. Often surgical stimulation was associated with this rapid respiration.

Laryngospasm and bronchospasm were not precipitated by the administration of Fluothane. Pharyngeal and laryngeal reflexes were depressed soon after induction, allowing the safe insertion of a nasopharyngeal or oropharyngeal airway. In "surgical" planes of anesthesia manual inflation of the lungs was accomplished easily. The drug was employed advantageously in 40 patients having a definite history of asthma. Eight of these patients had rales and rhonchi throughout the lung fields at the time of administration. In no patient did the asthmatic condition become worse clinically.

Cardiovascular System.—Tachycardia during administration of Fluothane was rare. The trend appeared to be towards a slowing of the pulse rate. In 49 (3.5 per cent) patients in this series, the decrease in pulse rate was greater than 20 per minute (table 4). In 41 patients (2.9 per cent) a bradycardia of less than 60 beats per minute was seen. These figures are less than those reported by other investigators. It is believed that in this series a greater incidence of bradycardia was prevented by the administration of adequate doses of anticholinergic drugs preoperatively. An increase in parasympathetic tone, as occurs presumably with the administration of cyclopropane, was thought to be the cause of bradycardia.

A decrease in blood pressure was common, though by no means invariable, during induction with Fluothane. It was noted (table 5)

TABLE 4

REDUCTIONS IN PULSE RATE DURING FLUOTHANE ADMINISTRATION

Pulse Rate Drop	Number	Per Cent
More than 20 per minute	26	1.8
More than 34 per minute	10	0.7
More than 40 per minute	8	0.6
More than 50 per minute	5	0.4
	49	3.5
Bradycardia less than 60 per minute	41	2.9

TABLE 5

HYPOTENSION GREATER THAN 20 MM. OF MERCURY DURING INDUCTION

Blood Pressure Fall	Number	Per Cent
More than 20 mm. Hg	216	16.6
More than 30 mm. Hg	127	9.7
More than 40 mm. Hg	61	4.7
More than 50 mm. Hg	56	4.2
	460	35.2

that 460 patients (35.2 per cent) suffered a reduction in systolic blood pressure greater than 20 mm. of mercury. In 71 patients the hypotension was severe enough to demand specific therapy, such as stopping the Fluothane, or administering anticholinergic drugs or vasopressor compounds (table 6). Usually the blood pressure returned toward

TABLE 6

THERAPEUTIC MEASURES TO COMBAT HYPOTENSION DURING INDUCTION

Treatment	Number
Fluothane discontinued	18
Anticholinergic drug	24
Vasopressor drug	25
Blood transfusion	4

normal levels with the beginning of surgery. During maintenance of anesthesia a decrease in blood pressure greater than 20 mm. systolic occurred in 174 or 12.4 per cent of patients. Again this alteration was treated in one of several ways, dependent upon the particular circumstances in each case (table 7). In most of these latter patients Fluothane was not believed to be the primary etiologic factor precipitating

TABLE 7

THERAPEUTIC MEASURES TO COMBAT HYPOTENSION DURING OPERATION

Treatment	Number
Fluothane discontinued	9
Blood transfusion	60
Vasopressor drug	41
Anticholinergic drug	16
Traction reflex relieved	26

hypotension. Blood loss or traction reflexes were held responsible frequently.

The physiologic changes which lead to hypotension are not yet known definitively. There seems little doubt that the degree of hypotension is related closely to the concentration of Fluothane exhibited to the patient. Experimental evidence in the dog heart-lung preparation (17) indicates that a progressive decrease in myocardial output accompanies exposure to increasing concentrations of the drug. At the same time laboratory data (1) and clinical observations (2, 19) indicate that Fluothane produces peripheral vasodilatation. In this series the extremities of patients were warm and dry, with full bounding pulses, and resembled the condition that is seen following the administration of chlorpromazine intravenously. These observations suggest that a reduction in peripheral resistance accompanies Fluothane anesthesia and may be a significant factor in the production of hypotension. Whatever the factors involved, evidence is mounting (21, 22), in addition to our findings, that sudden exposure of the patient to relatively high concentrations of Fluothane can cause cessation of cardiac action. This realization renders mandatory the provision of means whereby Fluothane can be administered in controlled and accurate concentrations.

Central Nervous System.—Fluothane alone was capable of producing satisfactory hypnosis, analgesia and muscular relaxation for many operative procedures. In safe concentrations it provided a degree of muscular relaxation akin to what might be expected of cyclopropane in optimal concentrations. The analgesia provided by Fluothane developed rather slowly. On a number of occasions the patient appeared well anesthetized, with some associated intercostal paresis, but the surgical incision caused movement of the extremities. To the observer it looked as if the patient had been "playing possum." After about 30 minutes of inhalation, analgesia was adequate for any surgical trauma.

TABLE 8

LIVER FUNCTION (BROMSULPHALEIN DYE RETENTION)

More Than 5 Per Cent Retention in 45 Minutes	Number of Patients	Per Cent
Controls (51 patients)		
24 hours postoperative	22	43.1
5 days postoperative	7	13.7
Fluothane (51 patients)		
24 hours postoperative	20	39.2
5 days postoperative	6	11.8

Metabolism.—As far as could be determined, Fluothane was eliminated unchanged through the lungs. In clinical concentrations it appeared to have little effect on liver or kidney function. Twenty patients anesthetized with Fluothane, but who did not receive intravenous glucose, had serial determinations of blood glucose during operation.

In no case was there an unusual increase or decrease in blood sugar concentration. A series of 51 patients receiving Fluothane had Bromsulfalein determinations performed twenty-four hours and five days following anesthesia. The controls were a similar series of patients anesthetized with drugs regularly employed in this hospital, including ethyl ether, cyclopropane and thiamylal sodium. The majority of the operations in each group were designated as major procedures. Retention of dye occurred in both series (table 8) but not to a greater extent in the Fluothane group than in the controls.

Besides anesthesia and surgical trauma many factors may interfere with liver function. Results such as the above do not incriminate or absolve Fluothane from interference with liver metabolism. However, in the 1,400 cases under review, no patient was seen with clinical evidence of liver dysfunction following anesthesia. One patient showed no abnormalities in a battery of liver function tests performed after four anesthetics with Fluothane given within a period of two weeks. A patient from another institution who came to autopsy for reasons unrelated to anesthesia, but only a short time after four administrations of Fluothane for lengthy neurosurgical procedures, showed a normal liver and kidney parenchyma (20).

Preoperative Medication

Preoperative medication for Fluothane patients did not differ greatly from that prescribed when other anesthetic drugs were given. Apprehensive patients were administered a short acting barbiturate about two hours preoperatively. A narcotic drug, usually meperidine, 50 to 100 mg., was prescribed for most patients about one hour before induction. In one group of 50 patients the narcotic was omitted in order to see if less respiratory depression developed during Fluothane administration. No difference was observed clinically.

A particular effort was made to ensure that adequate amounts of anticholinergic drugs were administered preoperatively. In the majority of patients the drug was given either intramuscularly or intravenously, or a fraction by both routes, about ten to fifteen minutes prior to induction in the operating room suite. In this way maximum effectiveness at the right time was more certain. Atropine or Antrenyl were the drugs employed most commonly. For the average patient the dose of either drug was 0.6 mg. With this regimen the incidence of bradycardia less than 60 beats per minute was 2.9 per cent in this series. In a number of patients, when bradycardia and hypotension were associated during induction of anesthesia, the administration of an anticholinergic drug reversed both conditions.

Induction

The boiling point of Fluothane is sufficiently low (50.2 C.) to permit satisfactory vaporization by the open drop technique. This method

was employed in 105 children. Induction was rapid and associated with a short excitement stage in about 50 per cent of patients. The speed of induction was equivalent to, if not faster than, that possible with vinyl ether. The absence of secretions was remarkable. Fluothane was dropped on the mask with caution to prevent the rapid development of respiratory depression in the surgical stage of anesthesia. Because of the inability to supplement respiratory exchange with the open drop technique, it was concluded that the administration of Fluothane by this method should be limited to short periods, and that in all cases oxygen should be flowed in under the face-mask. An alternative and safer induction technique in children utilizing a nonrebreathing mask was practiced in 89 cases. Flowing equal quantities of nitrous oxide and oxygen, Fluothane was introduced slowly but continually. Induction was rapid and respiratory exchange could be assisted manually as soon as indicated. It is believed that the potency of Fluothane, combined with its minimal irritability, places it in the unique position of being the only anesthetic drug with which satisfactory induction and maintenance of anesthesia are possible in children using a nonrebreathing technique.

In adults two principal types of induction were employed. Early in the series it was decided, in a purely arbitrary manner, to anesthetize patients utilizing a flow of nitrous oxide, 2 liters, and oxygen, 2 liters, to vaporize Fluothane. A partial rebreathing technique in a circle or to-and-fro system was used. Such purely inhalation inductions could be accomplished in five to seven minutes, but usually included a definite excitement stage. This excitement stage was obviated or circumvented by beginning the induction with a sleeping dose of an ultrashort acting barbiturate. Therefore in most patients the administration of thiamylal sodium, 100 to 250 mg., preceded application of the mask to the face. Laryngospasm and bronchospasm were almost nonexistent during induction and salivary secretions were absent. Masseter relaxation and obtundation of pharyngeal and laryngeal reflexes occurred in two to three minutes, allowing insertion of an airway without reaction. A concentration of 2.0 to 3.0 per cent Fluothane was required usually to induce surgical anesthesia. Once surgery had begun, or sometimes earlier, this concentration was reduced. A diminution of respiratory exchange, which involved first the intercostal muscles, developed during induction and usually persisted during maintenance of anesthesia. Assisted or controlled respirations were necessary to maintain adequate ventilation.

Endotracheal intubation was performed in 58 per cent of the patients in this series. Approximately two-thirds of these patients were intubated with the aid of a single dose of succinylcholine (40 to 50 mg.) intravenously. Intubation under Fluothane alone was at times difficult because the effects of the drug were so evanescent. Adequate muscular relaxation was always present for exposure of the larynx and

insertion of the tube, but usually, unless the gas machine was reconnected within 45 seconds, the plane of anesthesia became so light that coughing and bucking on the tube occurred. This undesirable reaction was subdued by several inhalations of Fluothane. In many instances it was circumvented by transtracheal insertion of a topical analgesic prior to intubation.

Maintenance

Maintenance of anesthesia was smooth in the great majority of patients. Concentrations of Fluothane between 0.4 and 1.6 per cent were sufficient to maintain anesthesia with moderate muscular relaxation. Alterations in planes of anesthesia could be accomplished rapidly. If a patient showed signs of lightening anesthesia, increasing the concentration inhaled by 0.5 per cent for eight to ten respirations established a deeper plane. The plane of anesthesia could be lightened in the opposite manner.

In this series satisfactory muscular relaxation for lower abdominal surgery was obtained by Fluothane alone in safe planes of anesthesia. For upper abdominal procedures a slow drip of succinylcholine, 0.1 per cent solution, was required frequently to give the surgeon satisfactory operating conditions. When the hilum of the lung was being manipulated during intrathoracic operations, bucking on the endotracheal tube was observed unless small amounts of succinylcholine were administered intravenously.

d-Tubocurarine chloride was not administered in this series because of the pronounced hypotension which has been reported following injection (2). Gallamine triethiodide (Flaxedil) also was not used. Patients reacted to succinylcholine in a manner similar to that seen when it was administered with other anesthetic drugs.

Bleeding or oozing of cut surfaces did not appear greater with Fluothane than with other drugs. However, it was our impression that patients under Fluothane reacted more readily to moderate blood loss by a fall in blood pressure. The peripheral vasodilatation associated with administration of this drug could account for this impression. The situation was similar to, but less marked than that seen with ganglionic blocking drugs.

It was observed that traction reflexes initiated by severe gastrointestinal manipulation or by pulling on the uterus often induced hypotension during Fluothane administration. The blood pressure returned toward normal when traction or manipulation was stopped.

Recovery

Emergence from anesthesia following Fluothane administration was satisfactory. In the typical patient pharyngeal and laryngeal reflexes returned within two to three minutes. Within five minutes the

patient answered questions, was oriented as to time, place and person and obeyed simple requests. Recovery room nurses noted that patients receiving Fluothane were able to return to their wards sooner than those receiving other anesthetics.

Nausea and vomiting in the postoperative period were uncommon. In this series 406 patients were followed closely in this regard. Of this group 3.2 per cent were nauseated and 4.7 per cent exhibited both nausea and vomiting.

Shivering was noted occasionally in the recovery room. No obvious explanation for this was apparent, although it is believed that the presence of peripheral vasodilatation during anesthesia with associated heat loss could reduce body temperature and account for shivering postoperatively.

Discussion

Fluothane is potentially a dangerous drug because it is an extremely potent, nonirritating compound. Its potency dictates that certain safeguards be taken regarding administration to patients. Precautionary measures include:

(1) The administrator must realize that a narrow margin of concentration may spell the difference between optimum effect and overdosage. This drug is not like a mild beer which is consumed in tall glasses. It resembles a potent liqueur which provides satisfaction in small quantities.

(2) Fluothane can be administered safely only when accurate means of vaporization are available. Vaporizers should be calibrated for Fluothane before they are used and should be so constructed that concentrations can be varied in tenths of one per cent over the range of clinical usefulness, that is, 0.1 to 3.5 per cent.

(3) The flow of gas which is vaporizing fluothane should be known at all times. This stipulation means that, if a circle system is being utilized, the Fluothane vaporizer must be placed between the gases being supplied from the gas machine and the inlet to the circle system. This point can be exemplified best by the following case report, which is the only case of cardiac arrest in this series:

A 30-year-old man weighing 118 pounds and in good physical condition underwent a right ureteral exploration for persistent right lower quadrant pain. Preoperatively blood pressure was 118/60 and pulse rate was 80 per minute. Premedication consisted of secobarbitol, 100 mg., meperidine, 100 mg., and atropine, 0.6 mg. Anesthesia was induced with thiopental sodium, 120 mg., following which the patient was administered nitrous oxide, 2 liters per minute and oxygen, 2 liters per minute, with Fluothane being vaporized by means of a standard Heidbrink ether bottle, with wick inserted, which was placed on the inhalation side of a standard circle system of a Heidbrink kinetometer. The concentrations of Fluothane being administered were unknown (this case occurred early in the series). Endotracheal intubation was facilitated by the injection of succinyl-

choline, 50 mg., intravenously. Anesthesia with nitrous oxide, oxygen and Fluothane proceeded uneventfully for one and one-half hours. The spontaneous respirations of the patient were assisted by the anesthesiologist during this period. When peritoneal closure was to begin, a succinylcholine drip, 0.1 per cent, was begun in order to provide maximal relaxation. At the same time controlled respirations were instituted to assure adequate ventilation. Within two minutes no pulse and blood pressure were obtainable. A thoracotomy was performed rapidly. The heart was found in asystole, but responded immediately to massage. The patient made an uneventful recovery.

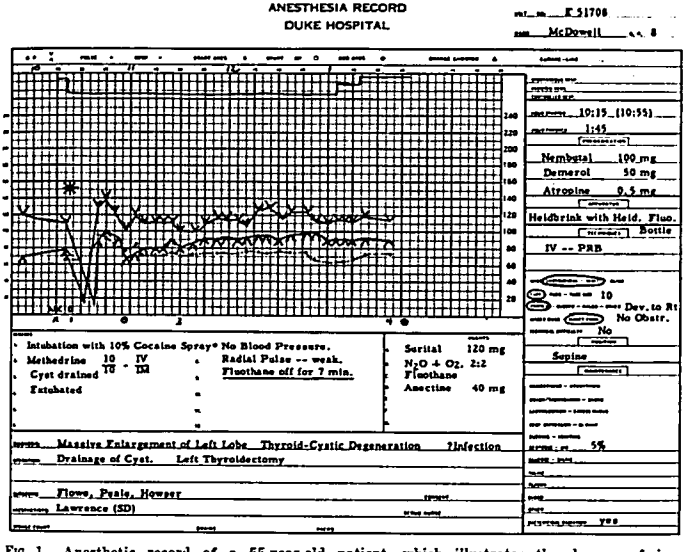

FIG. 1. Anesthetic record of a 55-year-old patient, which illustrates the danger of incorporating a Fluothane vaporizer into the circle system of an anesthetic gas machine.

In reconstructing the above events, it was believed that the instigation of controlled respirations just before the arrest suddenly increased the minute volume respiration, and, therefore, also increased the amount of gas passing over the surface of the Fluothane, so that a sudden increase in concentration of Fluothane was pumped into the lungs and blood stream of the patient.

An attempt was made to reproduce the situation just described. A new Heidbrink vaporizer designed specifically for Fluothane, and calibrated accurately for known rate of flow was incorporated into the circle system. Figure 1 shows the anesthetic record of this patient.

After a short induction with thiamylal sodium, nitrous oxide, oxygen and Fluothane, succinylcholine, 40 mg., was injected intravenously to facilitate intubation. Controlled respiration with unknown tidal or minute volume was instituted for two minutes without altering the concentration of Fluothane (approximately 1 per cent at a flow of 6 liters per minute) and intubation performed. Following insertion of the tube no blood pressure could be obtained, but a faint pulse was felt in the carotid area. The Fluothane was turned off and a vasopressor administered. The blood pressure was obtainable within a few minutes and the operation was begun. This same vaporizer, placed outside the circle system, was employed for similar procedures in numerous patients without severe episodes of hypotension.

(4) Probably the nonrebreathing technique is the ideal method in which to employ Fluothane. However, safe administration is practical utilizing the partial rebreathing technique if the vaporizer is not included in the circle system.

As experience grew with Fluothane, the contraindications to its use became less numerous. Due to the fact that in animals Fluothane sensitized the heart to epinephrine, the drug was not employed when epinephrine injections were contemplated by the surgeon for hemostasis. Because of the effect of the drug on the cardiovascular system, which is not yet defined clearly, it was not administered to patients in shock, to those with obvious diminished cardiac reserve, or when severe arrhythmias were present preoperatively. Uncomplicated hypertension was not a contraindication to the use of Fluothane.

Conclusions and Summary

Fluothane is a potent nonflammable and nonexplosive anesthetic drug which has been employed in all age groups and for a variety of operative procedures. Depression of the tidal volume of respiration occurs in surgical planes of anesthesia. Hypotension is prone to develop during induction of anesthesia. Accurate and proper methods of vaporization are essential if it is to be utilized safely. Much more investigation is required before its true status in anesthesia can be established. Work should proceed both in the laboratory and in the operating room. At the present time we believe that Fluothane will find a useful place in anesthesiology.

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